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# Large-Scale Synthesis of Crystalline 1,2,3,4,6,7-Hexa-*O*-acetyl-L-glycero- $\alpha$ -D-manno-heptopyranose

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*Dedicated to Professor Peter Stanetty on the occasion of his 70th birthday*

**Keywords:** Synthetic methods / Carbohydrates / Rare sugars / Indium / Allylation

The higher-carbon sugar L-glycero-D-manno-heptose is a major constituent of the inner core region of the lipopolysaccharide (LPS) of many Gram-negative bacteria. All preparative routes used to date require multiple steps, and scalability has been rarely addressed. Here a highly practical

synthesis of crystalline 1,2,3,4,6,7-hexa-*O*-acetyl-L-glycero- $\alpha$ -D-manno-heptopyranose by a simple four-step sequence starting from L-lyxose is disclosed. Only two recrystallisations are required and the process was demonstrated on a >100 mmol scale, yielding 41 g of the target compound.

## Introduction

Microorganisms are able to generate a variety of sugars that are absent in vertebrate organisms. Among these, L-glycero-D-manno-heptose (**1**, L,D-heptose) has been identified as a major constituent of the lipopolysaccharide (LPS) of Gram-negative bacteria, an important mediator for numerous interactions with the native and adaptive immune system of the host.<sup>[1]</sup> The highly conserved inner core region based on heptose **1** and 3-deoxy-D-manno-2-octulosonic acid (Kdo) and exhibited in many enterobacterial strains is illustrated in Figure 1.<sup>[1b]</sup> Structures containing L,D-heptose **1** have, for example, been studied in terms of binding to the cross-reactive antibacterial monoclonal antibody WN1 222–5,<sup>[2]</sup> interactions with C-type lectins<sup>[3]</sup> and in their roles as potential diagnostic tools for bacterial infections.<sup>[4]</sup>

Several different synthetic approaches to the synthesis of **1** were developed<sup>[5]</sup> and have recently been reviewed.<sup>[1a]</sup> Among those, two approaches have been widely taken up by the carbohydrate community (Figure 2). The first relies on the preferential *syn*-addition of Grignard reagents<sup>[5c,6]</sup> to the C-6 aldehyde moiety of suitably protected manno-pyranoside species such as **2**. The second is based on osmium-mediated diastereoselective dihydroxylation of an un-

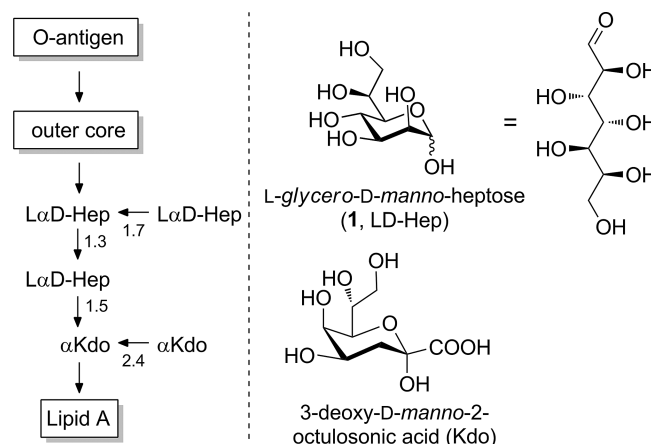


Figure 1. Representative structure of inner-core-region LPS containing L,D-heptose **1** (phosphorylation not shown).

saturated sugar such as **3**.<sup>[5b,7]</sup> Both approaches made use of D-mannose or simple D-mannosides as starting materials, requiring a series of chemical steps and (chromatographic) purifications. In particular, the first approach was further developed to facilitate concomitant installation of protecting or activating groups (thioglycosides).<sup>[6b,6c,8]</sup> Scalability was only addressed in one report in which methyl L-glycero- $\alpha$ -D-manno-heptopyranoside was prepared in seven to 10 steps from methyl  $\alpha$ -D-mannoside, with a combined yield of ca. 50%.<sup>[9]</sup> More recently, a de novo synthesis of orthogonally protected versatile heptosyl building block **4** in 10–11 steps was reported by the Seeberger group<sup>[10]</sup> and subsequently applied to the assembly of LPS inner core oligosaccharides.<sup>[4,11]</sup>

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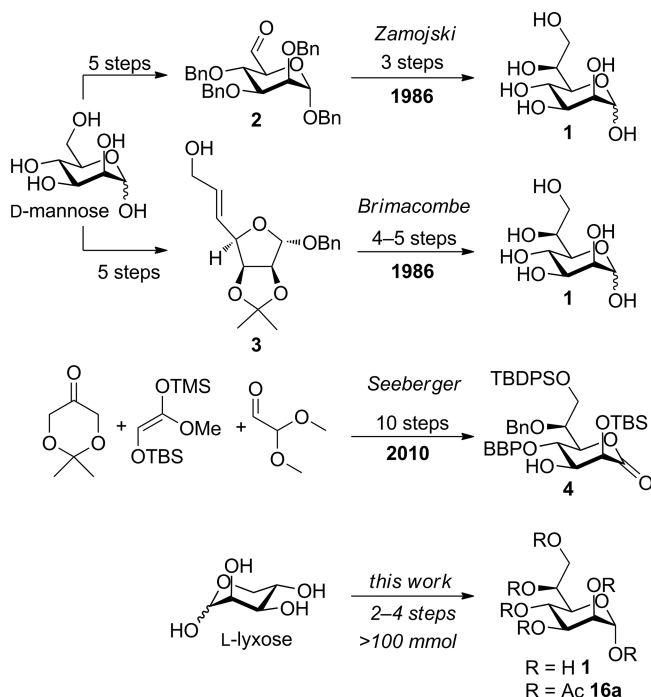
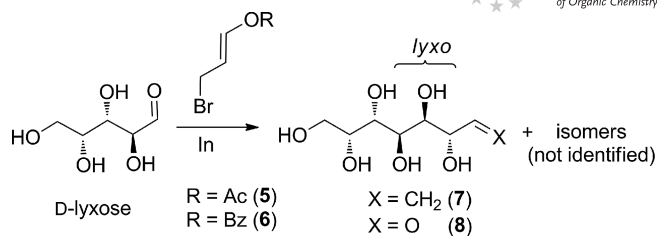


Figure 2. Preparative routes to *L*-glycero-*D*-manno-heptose (**1**) and derivatives.

Despite their chemical elegance and the inherent value of the final oligosaccharide structures, the approaches described above constitute specific solutions rather than a general answer to the availability of this important bacterial sugar. Consequently, a short, robust and scalable route to *L*-glycero-*D*-manno-heptose (**1**) is still not available, which constitutes a significant barrier to entry into this important field for synthetic chemists and biologists, as well as for commercial suppliers. In view of this, we set out to develop a reliable and scalable route to a crystalline and stable storage form of *L*-glycero-*D*-manno-heptose. It is noteworthy that to date synthetic studies are still being conducted starting from **1** or from its simple derivatives.<sup>[3b,12]</sup>

A comprehensive review of the literature revealed an indium-mediated diastereoselective acyloxyallylation of unprotected aldoses as a potential solution. The Madsen group had demonstrated that bromopropenyl esters **5** and **6** can be added to the aldehyde function of unprotected reducing sugars.<sup>[13]</sup> This transformation could deliver four stereoisomers; however, the isomer with the *lyxo* configuration was generally formed with good selectivity. The *lyxo* configuration corresponds to *anti*-addition of the indium organyl to the carbonyl group with a *syn* orientation with respect to the stereocentre at the former C-2 (see Scheme 1).

Although the preferential *anti*-addition to saturated aldehydes had been well established,<sup>[14]</sup> the *syn* configuration in respect to the closest stereocentre in the starting material is more specific to the use of unprotected aldoses.<sup>[15]</sup> When D-lyxose was used in this study, *D*-glycero-*L*-manno octenitol (**7**) was identified as the main stereoisomer after deacetylation and purification by RP-HPLC. Its identity was confirmed by transformation into *D*-glycero-*L*-manno-heptose



Scheme 1. Indium-mediated acyloxyallylation to D-lyxose.<sup>[13]</sup>

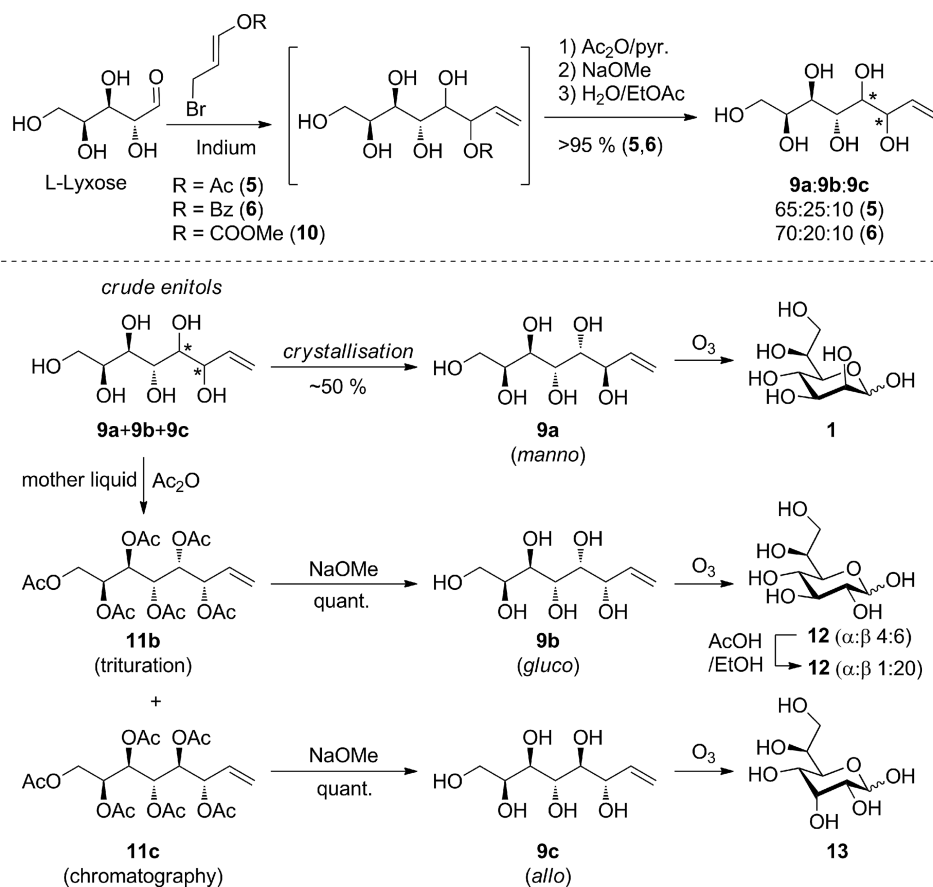
(**8**, the enantiomer of **1**). Because *L*-lyxose is commercially available in bulk quantities it is a reasonable starting material and we set out to develop this proof of concept study into a short and scalable process for the preparation of **1**, the final goal being a stable, crystalline and nonhygroscopic material for purposes of easy handling, shipping and long-time storage.

## Results and Discussion

At the beginning of our investigation D-lyxose was used, due to its lower cost and enabling of a direct comparison to the literature. All relevant findings were subsequently successfully reproduced with *L*-lyxose, and for the sake of clarity in the following discussion the structures of the *L*-series are consistently depicted.

3-Bromopropenyl acetate (**5**) and benzoate derivative **6** were each prepared in one step from acrolein and the appropriate acid bromide.<sup>[14b]</sup> These were treated with lyxose and indium according to the original Barbier-type procedure.<sup>[13]</sup> The protocol is synthetically easy, because it does not require any special precautions such as exclusion of air or moisture. However, effective stirring was identified as a critical requirement to achieve complete conversion of the lyxose. Insufficient stirring led to substantially lower formation of the addition products due to the competing Wurtz-type coupling of the reagent/and or its hydrolysis under the progressively acidic reaction conditions.<sup>[16]</sup> An excess of the bromopropenyl ester species (3 equiv.) and indium (2 equiv.) was originally applied to achieve full conversion to the addition products. Because the original Madsen report only identified the main isomer we set out to investigate the transformation in more detail. To this end, the crude monoesters were peracetylated to allow extractive separation from the inorganic byproducts. Subsequent deacetylation and separation of the reagent-derived lipophilic products by distribution between water and organic solvent delivered representative enitol mixtures. These were analysed with respect to their isomeric compositions by <sup>1</sup>H NMR spectroscopy (Scheme 2 and the Supporting Information).

In contrast with the original report,<sup>[13]</sup> only a small increase in selectivity towards the target *manno*-isomer **9a** was observed when 3-bromopropenyl benzoate (**6**, pure *E* isomer or *E/Z* mixture) was used as a replacement for 3-bromopropenyl acetate (**5**, *E/Z* ca. 6:4). Furthermore, almost quantitative recovery of the enitol mixture (60% in the literature) could be achieved. It was consistently made

Scheme 2. Isolation and identification of the three octenitols **9a–c**.

up of three isomers: the target *manno* isomer **9a** (65–70%), the *gluco* isomer **9b** (20–25%) and the *allo* isomer **9c** (10%). Over the course of the investigation pure reference material for **9a/9b/9c** was obtained and allowed their unambiguous quantification and the determination of their configurations (vide infra). The benzoyl bromide needed for the preparation of **6** is significantly more expensive than acetyl bromide (for **5**), and the use of **6** further complicated extractive purifications of the initially formed monoesters. A comparative investigation into the use of the more stable 3-bromopropenyl methyl carbonate<sup>[17]</sup> (**10**) showed substantially lower levels of conversion (<50%) of lyxose and was not further investigated. All further optimisation was thus performed with 3-bromopropenyl acetate (**5**).

Advantageously, the solubility of the desired *manno*-enitol **9a** in MeOH and EtOH is very low in relation to the other two isomers, allowing its isolation in ca. 50% yield by simple trituration from MeOH or EtOH. Pure **9a** could also be obtained in comparable yield by recrystallisation from MeOH without prior extractive removal of the nonpolar byproducts. To identify the other enitols **9b** and **9c**, the content of the mother liquids of these crystallisations was acetylated and the corresponding peracetates **11b** and **11c** were isolated by chromatographic separation and trituration. Reference material for **9b** and **9c** was obtained by deacetylation, and the configurations of all three isomers were determined by conversion into the corresponding heptoses **1**,

**12** and **13** by ozonolysis (Scheme 2) and analysis of the relevant  $^1\text{H}$ – $^1\text{H}$  coupling constants in the  $^1\text{H}$  NMR spectra. The remarkably low solubility of *gluco*-configured **11b** and **12** even allowed for the scalable preparation of **12** at a later stage.<sup>[18]</sup>

For the large-scale synthesis of *L*-glycero-*D*-manno-heptose (**1**) a more step-economic process without the reagent-intensive acetylation/deacetylation sequence was aspired to. Consequently, the hydrolysis of the acetate and the separation of all organic and inorganic ( $\text{InBr}_3$ ) byproducts had to be accomplished at the stage of the polar species **9a** or its monoacetate. Conventionally, the quantitative separation of indium from aqueous solutions is performed by precipitation of indium ( $\text{In}(\text{OH})_3$  (basic media) or indium sulfide (with  $\text{H}_2\text{S}$ );<sup>[19]</sup> the latter was not considered viable due to the toxicity and stench of the required reagents. The use of solid-supported thiourea (QP-TU) led to significantly lower isolated yields of **9a**. Precipitation of  $\text{In}(\text{OH})_3$  and concomitant deacetylation was achieved with different bases ( $\text{NH}_3$ ,  $\text{K}_2\text{CO}_3$ , triethylamine, NaOMe) in water and mixtures with lower alcohols. The use of triethylamine (TEA) in particular was beneficial because it is volatile and extractable into organic solvents, and the corresponding salts  $\text{TEA}\cdot\text{HBr}$  (3 equiv.) and  $\text{TEA}\cdot\text{OAc}$  (1 equiv.) are highly soluble in  $\text{CHCl}_3$  and MeOH, allowing their separation concomitantly with the stereoisomers **9b** and **9c** by trituration and recrystallisation. Several attempts to separate the fine, gelat-

inous  $\text{In}(\text{OH})_3$  by filtration (with and without filter aids) turned out to be troublesome even at small scale. On the contrary, separation of  $\text{In}(\text{OH})_3$  by centrifugation worked reliably at different scales (1–100 mmol) with use of standard benchtop centrifuges. The isolated yields of pure **9a** obtained by this route were slightly lower (ca. 44%) than those provided by the acetylation/deacetylation procedure (49%), which was attributed to loss of material in the centrifugation residue and reduced crystallisation yields in the presence of the inorganic salts (see Figure 3). For small-scale preparation of **9a** the acetylation/deacetylation procedure (route A) is more efficient, whereas the second route is recommended and was used for the preparation of **9a** at larger scale (300 mmol lyxose).

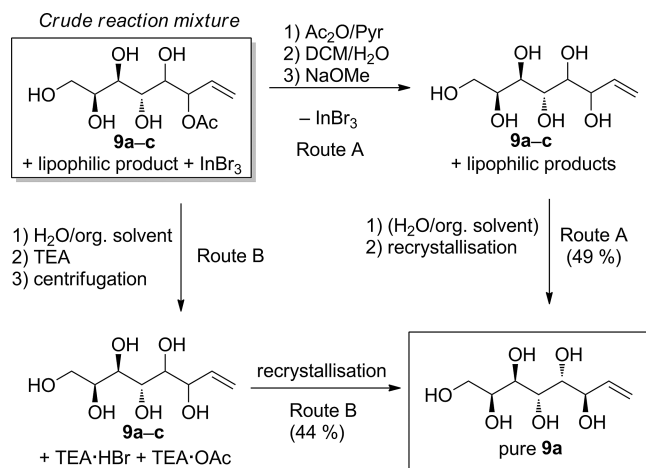
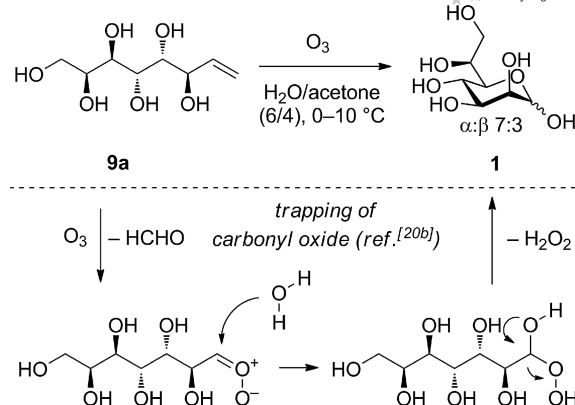


Figure 3. Alternative ways of obtaining pure *manno*-octenitol **9a**.

### Development of a Scalable Ozonolysis Protocol

Standard ozonolysis of **9a** at low temperature in  $\text{MeOH}$ <sup>[13]</sup> was initially applied to generate **1** and to confirm its *manno* configuration. However, the low solubility of **9a** in  $\text{MeOH}$ , the low reaction temperature and, in particular, safety concerns with respect to the accumulation of the corresponding hydroperoxides limit the scalability of such protocols. New protocols minimising the formation of peroxide species have recently been reported.<sup>[20]</sup> It was shown that when alkenes were subjected to ozonolysis in mixtures of water and organic solvents (e.g., acetone), water traps the transient carbonyl oxides,  $\text{H}_2\text{O}_2$  is released in stoichiometric amounts, and the formation of peroxides is minimised (see Scheme 3, lower part).

Our attempts at the ozonolysis of water-soluble starting materials such as **9a** required some alterations to the original conditions. A water/acetone ratio of ca. 60:40 was optimal to achieve high solubility of **9a** and still allow the use of lipophilic Sudan III as a convenient indicator for monitoring the consumption of the starting material. At temperatures  $<10^\circ\text{C}$ , fast conversion of **9a** to **1** was achieved, whereas at higher temperatures or higher water content significantly slower conversion was observed. The decomposition of  $\text{H}_2\text{O}_2$  was most conveniently accomplished with



Scheme 3. Ozonolysis to afford **1**, together with putative mechanism<sup>[20b]</sup> of the decomposition of the transient carbonyl oxide.

$\text{PPh}_3$  (solubilised by addition of acetone), leading exclusively to lipophilic byproducts that were easily removed by extraction with organic solvents and allowed the isolation of pure **1** from the aqueous layer.<sup>[21]</sup>

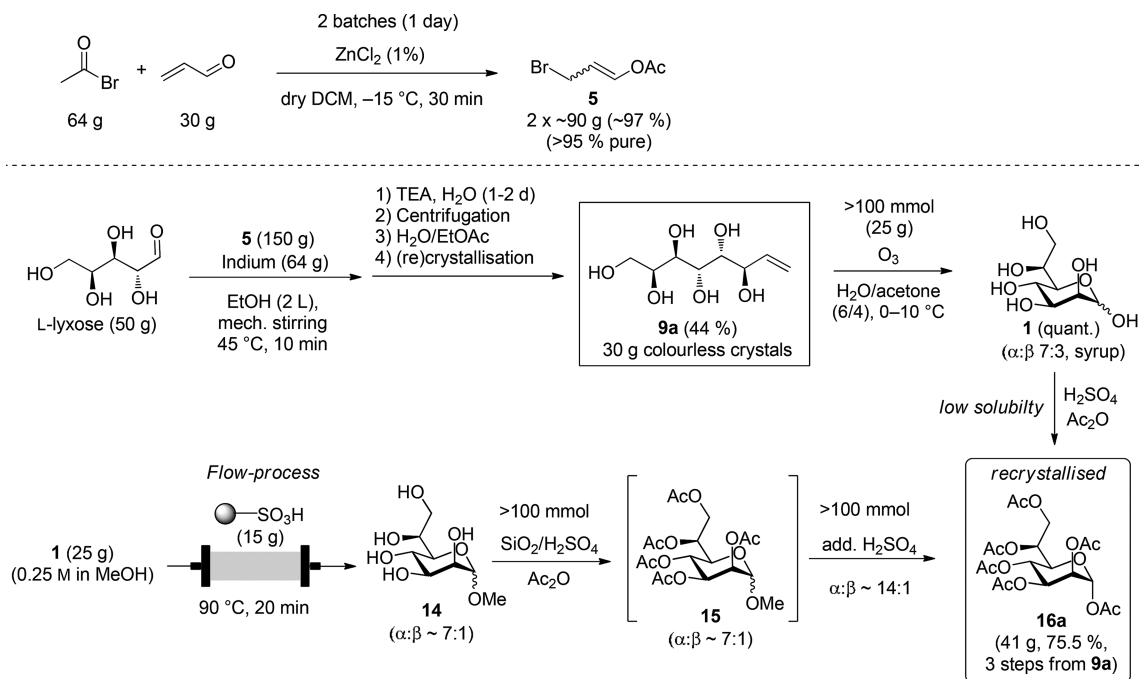
### Large-Scale Preparation of $\alpha$ -Pyranosyl Peracetate **16a**

In order to provide quick and reliable access to the required quantities of 3-bromopropenyl acetate (**5**), the reported procedure from acrolein and acetyl bromide with  $\text{ZnCl}_2$  as catalyst was slightly modified.<sup>[14b]</sup> Commercial quality (stabilised) acrolein was shown to work equally well as distilled acrolein. At increased concentration and scale the temperature profile of the reaction deserved closer consideration. At temperatures below  $-30^\circ\text{C}$  the addition of  $\text{ZnCl}_2$  gave no reaction. Upon warming to  $-20^\circ\text{C}$  the reaction initiated, with onset of a rapid increase in temperature. Under these circumstances, the largest experiments with acceptable temperature rise (from  $-20$  to  $+15^\circ\text{C}$ ) were conducted at 550 mmol scale at 2.5 M concentration. A modified aqueous workup delivered **5** as a dark coloured liquid (*E/Z* 6:4) in excellent yield (90 g,  $>95\%$ ) and purity (ca. 95%). It was stable for several weeks upon storage at  $-20^\circ\text{C}$ . Distillation (ca.  $80^\circ\text{C}$ , 1 mbar) or a quick passage over silica furnished **5** as a colourless liquid. However, in both cases 20–30% loss of material (consistent with the reported yields<sup>[14b]</sup> of 60–70%) without any increase in purity ( $^1\text{H}$  NMR; see the Supporting Information) or change in the performance of the reagent was seen.

Acetoxyallylation of L-lyxose at larger scale was performed at a concentration of 2.5% (w/v) lyxose in EtOH (maximum solubility at  $50^\circ\text{C}$  ca. 3%). At this scale, indium was added first to minimise exposure of **5** to solvent and heat and the reaction was started by the addition of **5** at ca.  $45^\circ\text{C}$  to limit the exotherm (ca.  $61^\circ\text{C}$ ). A detailed reproducible protocol for preparation of 30 g of pure crystalline **9a** as a single batch (Scheme 4) is included in the Experimental Section.

Under optimised conditions (vide supra), enitol **9a** (up to 25 g) was subjected to ozonolysis as a single batch to furnish pure L,D-heptopyranose **1** within 4–5 h in quantita-





Scheme 4. Convenient and scalable preparation of pure  $\alpha$ -pyranosyl peracetate **16a** (41 g) in four single-batch operations.

tive yield as a mixture of anomers ( $\alpha/\beta$  7:3). Heptose **1** is typically isolated as a hygroscopic syrup;<sup>[5b]</sup> however, a solid foam could be obtained by repeated concentration from *i*PrOH. Attempted anomerisation of **1** with AcOH in *i*PrOH (compare **12**<sup>[18]</sup>) led to a filterable powder although without anomeric enrichment. However, the solid foam and powder remain hygroscopic and are only stable under exclusion of atmosphere. Because our ideal target was a crystalline and bench-stable storage form of **1**, solid peracetate **16a** was selected, because it constitutes a versatile starting material for the preparation of thioglycosides,<sup>[12a]</sup> heptosyl phosphates<sup>[22]</sup> or glycosyl donors such as imidates<sup>[23]</sup> or bromides.<sup>[24]</sup> The direct conversion of **1** into the corresponding pyranose peracetates **16a** and **16b** under either basic<sup>[5a,25]</sup> or acidic<sup>[5b]</sup> (H<sub>2</sub>SO<sub>4</sub>) conditions has been reported, the latter giving almost pure  $\alpha$ -pyranose form **16a** on prolonged stirring in Ac<sub>2</sub>O/AcOH. However, in our experience this reaction is sluggish (days) at larger scale and its rate is highly dependent on the physical appearance of **1** (solid foam vs. syrup). This technical but important issue was attributed to the low solubility of **1** in Ac<sub>2</sub>O, AcOH and mixtures thereof.<sup>[26]</sup> A two-step strategy based on initial formation of methyl heptoside **14** and a concomitant acetylation/acetolysis step turned out to be more reliable. Fischer-type glycosylation of **1** with MeOH (with DOWEX™ 50 H<sup>+</sup> resin at reflux overnight) has been reported before and delivers high proportions of the methyl pyranosides **14**.<sup>[23a]</sup> Alternatively, the same transformation was achieved conveniently, more rapidly and with substantially less catalyst in a continuous-flow process. A standard Vapourtec system with a heated column reactor filled with QP-SA beads was used to optimise the reaction conditions (see the Supporting Information). An optimum of space/time yield and

composition was found at 90–100 °C and with 10–25 min residence time. Simple concentration furnished the crude methyl heptosides **14** ( $\alpha$ -pyranoside/ $\beta$ -pyranosides ca. 7:1, with ca. 3–5%  $\alpha$ -furanoside), which were directly subjected to acetylation and acetolysis in a one-pot process.<sup>[12c]</sup> Catalytic amounts of SiO<sub>2</sub>/H<sub>2</sub>SO<sub>4</sub><sup>[27]</sup> in Ac<sub>2</sub>O rapidly furnished the acetylated methyl heptosides **15** with no change in the anomeric composition, and addition of sulfuric acid (ca. 0.6 equiv.) resulted in complete acetolysis overnight, delivering  $\alpha$ -pyranose peracetate **16a** almost exclusively ( $\alpha/\beta$  >14:1) and in a reliable and scalable manner. Crude mixtures obtained in this way solidified on concentration, and pure  $\alpha$ -peracetate **16a** was isolated by a single recrystallisation from EtOH in an overall yield of 75.5% (three steps from **9a** at 41 g scale). A second crop of pure **16a** (3.9 g, 7.2%) was collected after anomerisation of the mother liquor in Ac<sub>2</sub>O/AcOH with prolonged stirring with H<sub>2</sub>SO<sub>4</sub> (3 d).

## Summary and Conclusion

A highly practical process affording crystalline anomerically pure 1,2,3,4,6,7-hexa-*O*-acetyl-L-glycero-D- $\alpha$ -mannoheptopyranose (**16a**) in only four simple steps from L-lyxose was developed. No chromatographic separation and only two simple recrystallisations are required. The preparation can be reproducibly performed on a >100 mmol scale delivering 41 g of this bench-stable, nonhygroscopic storage form of L-glycero-D-manno-heptose (**1**).

## Experimental Section

**General:** All starting materials and reagents were purchased from commercial sources and used without further purification. The ini-

tially used indium was standard powder from Alfa Aesar; for the scale-up 325 mesh quality from American Elements was used. Dry dichloromethane was obtained by use of the Innovative Technology Inc. solvent purification system and stored over molecular sieves (4 Å). The ozone was produced from pure O<sub>2</sub> with a LAB2B ozone generator (Triogen Ltd.). Reactions were monitored by TLC on silica gel 60 F254 plates; spots were visualized by dipping with anisaldehyde/sulfuric acid and heating. Normal-phase column chromatography was performed on commercial cartridges with a Biotage Isolera Four and gradients of hexane/EtOAc. NMR spectra were recorded with Bruker Avance 400, Varian V NMR S-600 or Varian V NMR S-700 instruments and are calibrated to the residual solvent according to the literature.<sup>[28]</sup> Assignments are based on DEPT-135, COSY, HSQC and HMBC spectra. Low- and high-resolution mass spectrometry was performed by use of the indicated techniques on Waters LCT Premier XE or Waters TQD instruments equipped with Acquity UPLC and a lock-mass electrospray ion source. Optical rotations were recorded with a Schmidt+Haensch Polartronic H 532 instrument and a 100 mm length cell. Elemental analysis was performed with an Exeter CE-440 Elemental Analyser. Melting points were recorded with an Optimelt automated melting point system with a heating rate of 1 °C min<sup>-1</sup> (70% onset point and 10% clear point).

**L-glycero-D-manno-Heptose (1):** Enitol **9a** (25.3 g, 121.5 mmol, 1.0 equiv.) was dissolved in water/acetone (300/200 mL), giving a slightly turbid solution. A small amount of Sudan red (III) in acetone was added, staining the mixture pink, and the reaction mixture was cooled with an external ice bath. When the internal temperature reached 15 °C, bubbling of ozone through the reaction mixture through a sintered gas inlet was started. The reaction mixture was kept at ca. 10 °C and had decolourised after around 4.5 h. Analysis by TLC (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O 14:6:1) confirmed complete conversion of starting material to the target compound, together with a slightly more apolar shadow that vanished during the reductive workup. Upon complete conversion the ozone generator was switched off, and oxygen was passed through the reaction for 30 min, after which PPh<sub>3</sub> (70 g, ca. 2 equiv.) and additional acetone (200 mL) were added (to solubilise the PPh<sub>3</sub> and to facilitate the reduction) and the mixture was stirred at room temp. overnight. After 3 h no peroxides were detectable (peroxide test strip), which was confirmed the next morning. The reaction mixture was concentrated (200 mbar), and the aqueous residue (insoluble white solid) was washed with CH<sub>2</sub>Cl<sub>2</sub> (300–200 mL; addition of EtOAc helped phase separation at this high concentration), giving all the re-established red colour of Sudan III in the organic layer. The aqueous layer was washed with EtOAc (200 mL), giving clear solutions, with Et<sub>2</sub>O and once with hexane. The aqueous layer was concentrated and twice reconcentrated from MeOH to give a residue (36 g) that was directly subjected to the formation of methyl heptosides **14**. A homogeneous aliquot was analysed by <sup>1</sup>H NMR to show the target compound as an anomeric mixture (α/β ca. 7:3) as the only constituent, identical to an authentic material obtained by saponification of **16a** and with data consistent with the literature.<sup>[5a]</sup> Physical properties: <sup>1</sup>H NMR (600 MHz, D<sub>2</sub>O, ref. to MeOH = 3.34): δ = 5.16 (d, *J* = 1.5 Hz, 1 H, H1α), 4.86 (d, *J* = 0.9 Hz, 0.5 H, H1β), 4.02 (ddd, *J* = 7.1, 5.6, 1.3 Hz, 1 H, H6α), 3.97 (td, *J* = 6.6, 1.7 Hz, 0.5 H, H6β), 3.92 (dd, *J* = 3.3, 0.8 Hz, 0.5 H, H2β), 3.91 (dd, *J* = 3.2, 1.5 Hz, 1 H, H2α), 3.87–3.81 (m, 2 H, H3α, H4α), 3.78 (t, app, *J* = 9.8 Hz, 0.5 H, H4β), 3.76–3.73 (m, 1 H, H5α), 3.72–3.69 [m, 1 H, H7a (β), H7b (β)], 3.68 [dd, *J* = 11.4, 7.2 Hz, 1 H, H7a (α)], 3.64 [dd, *J* = 11.5, 5.5 Hz, 1 H, H7b (α)], 3.65–3.62 (m, 0.5 H, H3β), 3.32 (dd, *J* = 9.8, 1.7 Hz, 0.5 H, H5β) ppm. <sup>13</sup>C NMR (151 MHz, D<sub>2</sub>O, ref. to MeOH = 49.5): δ = 94.8 (C1α), 94.6 (C1β), 75.3 (C5β),

73.9 (C3β), 71.8 (C2β), 71.6 (C5α), 71.3 (C2α), 71.2 (C3α), 69.4 (C6α), 69.3 (C6β), 66.9 (C4α), 66.5 (C4β), 63.7 (C7α), 63.4 (C7β) ppm. HRMS (<sup>+</sup>ESI-TOF): calcd. for C<sub>7</sub>H<sub>14</sub>NaO<sub>7</sub> 233.0637 [M + Na]<sup>+</sup>; found 233.0632.

**(E/Z)-3-Bromopropenyl Acetate (5):** Acrolein (95%, not freshly distilled, 36.8 mL, 550 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (220 mL) and cooled to –40 °C (precipitation of a little white solid at ca. 5 °C), acetyl bromide (38.7 mL, 523 mmol, 0.95 equiv.) was added over 2 min, followed by ZnCl<sub>2</sub> (no pre-activation, 750 mg, 5.5 mmol, 0.01 equiv.) at –30 °C, and the reaction mixture was warmed by lowering the cooling bath (–45 °C). When the temperature started rising quickly (–20 °C) the flask was again submersed into the cooling bath to prevent overheating. The temperature rose to +15 °C, after which it dropped again, and the reaction mixture was stirred at around –20 °C for 30 min. An aliquot (20 min) was worked up (Et<sub>2</sub>O/NaHCO<sub>3</sub>) and concentrated (400 mbar) to confirm complete conversion of acrolein to the target compound. The reaction mixture was cooled to –30 °C and added to a mixture of water and ice (200 mL). Phases were separated, leading to a milky organic layer and a clear acidic aqueous layer; the bright yellow colour of the organic solution was completely lost. The organic layer was washed with water (still acidic) twice (back-extraction with CH<sub>2</sub>Cl<sub>2</sub>) and twice with NaHCO<sub>3</sub> and brine, dried with MgSO<sub>4</sub> and concentrated to leave crude material (92.1 g, 98.7%) as a brownish light liquid with a purity of 90–95% (<sup>1</sup>H NMR) and with spectroscopic data consistent with the literature.<sup>[14b]</sup> The material was used without further purification for the preparation of **9a**.

**1,2-Dideoxy-1-glycero-D-manno-oct-1-enitol (9a):** A solution of L-lyxose (50.3 g, 335 mmol, 1.0 equiv.) in EtOH (2 L) at 45 °C was prepared in a 5 L round-bottomed flask. Heating was removed and stirring was adjusted to ca. 350 rpm (mechanical stirrer), maintaining a significant vortex. First, indium (325 mesh, 63.8 g, 556 mmol, 1.66 equiv.) and directly afterwards crude 3-bromopropenyl acetate (**5**, ca. 95% pure, 150 g, 837.5 mmol, 2.5 equiv.) were added quickly. The colour changed from dark brown to ochre and the internal temperature rose after a short period of induction up to 63 °C. Some remaining indium was visible in the bottom of the flask but was moved rapidly at all times. Analysis by TLC (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O 14:6:1) after 10 min showed complete conversion of L-lyxose to the monoacetates with no indication of remaining L-lyxose or formed ethyl lyxoside (both staining green). The reaction mixture was filtered and concentrated (50 mbar). Small amounts of formed white crystals were shown to be inorganic. The residue (370 g, ca. 130 g of EtOH) was taken up in water (450 mL) and washed with CH<sub>2</sub>Cl<sub>2</sub> (400, 200 mL, back-extraction with 50 mL of water), and Et<sub>2</sub>O (200, 100 mL, back-extraction with 50 mL of water), leaving all colour in the CH<sub>2</sub>Cl<sub>2</sub> layer. Saponification without prior organic extraction led to the formation of more volatile and smelly components. TLC confirmed all target compounds in the aqueous layer. The residual aqueous solution (10–20% EtOH) was treated with TEA (240 mL), quickly leading to a white suspension; pH was confirmed to remain basic. The next morning a small sample was diluted with water, centrifuged and concentrated, showing ca. 6% of residual monacetate species (<sup>1</sup>H NMR). Stirring was continued for another day, giving complete deacetylation. The reaction mixture was treated with EtOAc (to separate excess of TEA) in a separating funnel (not necessary at lower concentration), after which the aqueous layer was transferred to centrifugation vessels and centrifuged (10000 rpm, 18000 g, 15 min), giving very good separation of a two-phasic solution and a white solid. The white solid was treated with fresh water (in total 500 mL) followed by centrifugation (2×). The clear supernatant phases were separated

in a separating funnel, and the aqueous layer was washed with fresh EtOAc,  $\text{CHCl}_3$  and hexane (facilitating the concentration of aqueous layers) before being concentrated. At this scale the removal of the last bit of water was difficult and was much facilitated by coevaporation with *i*PrOH to give a white slurry (330 g, ca. 30 mL of solvents). This material was triturated with MeOH (300 mL  $\rightarrow$  MeOH/ $\text{H}_2\text{O}$  10:1, 30 min), and the white solid was collected by filtration, washed with MeOH (2  $\times$  50 mL) and  $\text{Et}_2\text{O}$  (2  $\times$  50 mL) and dried to give target compound **9a** (28.3 g, 40.6%, >95% pure). It was taken up in MeOH/ $\text{H}_2\text{O}$  (10:1, 310 mL), heated to reflux temperature and stirred at room temp. overnight to give clean target compound as a white solid (26.1 g). The original filtrate was concentrated to give a white slurry that was treated with  $\text{CHCl}_3$  (200 mL) leading to two layers, which were separated, the lower one being mainly TEA·HBr. The upper layer was concentrated and triturated with  $\text{CHCl}_3$ /MeOH (200 mL + 50 mL) for 1 h to lead to a second fraction of white solid (10 g *manno:gluco* 6:4 + 10 mol-% TEA·HBr). This was recrystallized from MeOH (170 mL, addition of water until clear solution) to yield white, needle-like crystals (4.2 g, 95% pure) that were combined with the mother liquor from the main isolation procedure and recrystallized a second time (MeOH/water 9:1, 100 mL) to give a second crop of very clean target compound (4.5 g) as needle-shaped crystals, adding up to a total yield of 30.6 g (43.9%) of pure **9a**. Physical properties: m.p. 171.9–172.7 °C (MeOH/ $\text{H}_2\text{O}$ ),  $[\alpha]_{\text{D}}^{28} = +12$  ( $c = 0.6$ ,  $\text{H}_2\text{O}$ ) {ref.<sup>[13]</sup> for enantiomer **7**: m.p. 170–172 °C (EtOH);  $[\alpha]_{\text{D}}^{22} = -10.5$  ( $c = 2$ ,  $\text{H}_2\text{O}$ )}.  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$ , ref. to MeOH = 3.34):  $\delta = 6.01$  (ddd,  $J = 17.3$ , 10.5, 6.8 Hz, 1 H, H7), 5.37 (dt,  $J = 17.3$ , 1.3 Hz, 1 H, H8a), 5.30 (dt,  $J = 10.5$ , 1.2 Hz, 1 H, H8b), 4.21–4.16 (m, 1 H, H6), 3.97 (ddd,  $2 \times J = 5.9$ , 1.4 Hz, 1 H, H2), 3.93 (dd,  $J = 9.4$ , 1.1 Hz, 1 H, H4), 3.74 (dd,  $J = 8.2$ , 1.1 Hz, 1 H, H5), 3.70–3.66 (m, 3 H, H1a/H1b, H3) ppm.  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ , ext. ref. to MeOH = 49.50):  $\delta = 138.3$  (C7), 118.3 (C8), 73.1 (C6), 72.2 (C5), 70.9 (C2), 70.0 (C3), 69.0 (C4), 63.9 (C1) ppm. HRMS (+ESI-TOF): calcd. for  $\text{C}_8\text{H}_{16}\text{NaO}_6$  231.0845  $[\text{M} + \text{Na}]^+$ ; found 231.0844. Calcd. C 46.15, H 7.75; found C 46.12, H 7.72.

**1,2-Dideoxy-L-glycero-D-gluc-oct-1-enitol (9b):** Hexaacetate **11b** (10.00 g, 21.7 mmol) was suspended in MeOH (ca. 200 mL) and treated with NaOMe until pH ca. 12. Within ca. 6 h the reaction mixture became a clear solution and complete conversion was confirmed by TLC (hexane/EtOAc 1:1 and  $\text{CHCl}_3$ /MeOH/ $\text{H}_2\text{O}$  7:3:0.5). The reaction mixture was neutralised by addition of QP-SA and was filtered and concentrated to give the target **9b** as a white solid (4.5 g, quant.). Analytical samples were prepared by recrystallisation from pure EtOH or EtOH/water (10:1, 20 mL g $^{-1}$ , > 50% recovery), the latter giving big colourless crystals. Behaviour on melting point determination (fast vs. slow heating) and elemental analysis indicated a monohydrate. Physical properties: m.p. 126.8–127.7 °C (EtOH/ $\text{H}_2\text{O}$ ).  $[\alpha]_{\text{D}}^{28} = -6.0$  ( $c = 0.8$ ,  $\text{H}_2\text{O}$ ).  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$ , ref. MeOH = 3.34):  $\delta = 5.88$  (ddd,  $J = 17.6$ , 10.5, 7.4 Hz, 1 H, H7), 5.43–5.36 (m, 1 H, H8a), 5.32–5.26 (m, 1 H, H8b), 4.24 (app. t,  $J = 7.7$  Hz, 1 H, H6), 3.93 (ddd,  $J = 7.2$ , 5.9, 1.4 Hz, 1 H, H2), 3.76 (dd,  $J = 8.1$ , 1.1 Hz, 1 H, H5), 3.70 (dd,  $J = 9.4$ , 1.1 Hz, 1 H, H4), 3.71–3.63 (m, 3 H, H1a, H1b, H3) ppm.  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ , ref. to MeOH = 49.5):  $\delta = 136.8$  (C7), 119.2 (C8), 75.21 (C6), 72.9 (C5), 70.7 (C2), 70.1 (C3), 69.8 (C4), 63.9 (C1) ppm. HRMS (+ESI): calcd. for  $\text{C}_8\text{H}_{16}\text{O}_6$   $[\text{M} + \text{Na}]^+$ : 231.0845; found 231.0851. Calcd. (monohydrate): C 42.47, H 8.02; found C 42.48, H 7.93.

**Preparation of Reference Material for 9c:** From the mother liquid from the isolation of acetylated *gluco*-enitol **11b** the *allo*-isomer **11c** was isolated by column chromatography ( $\text{SiO}_2$ , Hex/EtOAc gradient 20% to 50%) contaminated with another species (ca. 15%),

probably another stereoisomer. Compound **11c** (500 mg, 1.08 mmol, ca. 85% pure) was dissolved in MeOH (ca. 10 mL) and treated with NaOMe until pH ca. 12. Within ca. 1 h complete conversion was confirmed by TLC (hexane/EtOAc 1:1 and  $\text{CHCl}_3$ /MeOH/ $\text{H}_2\text{O}$  7:3:0.5). The reaction mixture was neutralised by addition of QP-SA and was filtered and concentrated to give the target **9c** as an oil, together with an isomeric impurity (ca. 15%).  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$ , ref. to MeOH = 3.34):  $\delta = 5.98$  (ddd,  $J = 17.4$ , 10.5, 7.0 Hz, 1 H, H7), 5.41–5.30 (m, 2 H, H8a/H8b), 4.42–4.36 (m, 1 H, H6), 3.97 (ddd,  $J = 7.3$ , 5.3, 2.1 Hz, 1 H, H2), 3.86 (dd,  $J = 6.6$ , 4.8 Hz, 1 H, H5), 3.81 (dd,  $J = 6.8$ , 2.1 Hz, 1 H, H3), 3.76 (app. t,  $J = 6.7$  Hz, 1 H, H4), 3.70–3.61 (m, 2 H, H1a/H1b) ppm.  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ , ref. to MeOH = 49.5):  $\delta = 136.3$  (C7), 118.8 (C8), 75.0 (C5), 73.7 (C6), 72.2 (C4), 71.7 (C3), 71.3 (C2), 63.6 (C1) ppm.

**1,2-Dideoxy-L-glycero-D-gluc-oct-1-enitol Hexaacetate (11b):** The concentrated mother liquids from the crystallisations of **9a** (content of enitols ca. 30 g, 144 mmol) were dissolved in pyridine (150 mL).  $\text{Ac}_2\text{O}$  (120 mL, 1.3 mol, ca. 9 equiv.) was added by dropping funnel, leading to an increase in temperature (ca. 60 °C). The mixture was cooled with an ice bath for the first 30 min, after which DMAP (600 mg, 7.2 mmol, 0.05 equiv.) was added and the mixture was stirred for another 2 h. TLC (hexane/EtOAc 1:1) indicated the peracetylated enitols as dominant constituents with slightly more polar byproducts. More  $\text{Ac}_2\text{O}$  (20 mL) was added and the stirring was continued for another 1 h. A lot of white precipitate had formed, and this was collected by filtration and washed with acetone. The solid was separated between  $\text{CH}_2\text{Cl}_2$ /water, and the organic layer was washed with water, HCl (1 M),  $\text{NaHCO}_3$  and brine, dried with  $\text{Na}_2\text{SO}_4$ , concentrated (25 g) and triturated in hexane/EtOAc 4:1 (100 mL) to give a crude mixture with **11b** as major component (23 g, 17% impurities). Trituration from hexane/ $\text{CH}_2\text{Cl}_2$  1:1 (2  $\times$  ca. 200 mL) gave ca. 15 g of white solid, according to  $^1\text{H}$  NMR pure target compound **11b**. Analogous aqueous workup of the original filtrate, followed by trituration, gave only a small amount of white solid (ca. 4 g, *manno:gluco* 1:1). The *allo*-enitol **11c** constitutes the main component in the filtrates of these triturations. An analytical sample of **11b** was prepared by recrystallisation from MeOH. Physical properties: m.p. 178.9–179.8 °C (MeOH).  $[\alpha]_{\text{D}}^{28} = -6.0$  ( $c = 0.6$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ , ref. to  $\text{CHCl}_3 = 7.26$ ):  $\delta = 5.81$  (ddd,  $J = 17.0$ , 10.6, 6.1 Hz, 1 H, H7), 5.37 (dd,  $J = 9.4$ , 1.3 Hz, 1 H, H4), 5.36–5.29 (m, 1 H, H8a), 5.31 (br. s, 1 H, H8b), 5.28–5.25 (m, 1 H, H6), 5.24 (dd,  $J = 9.5$ , 1.5 Hz, 1 H, H3), 5.20–5.16 (m, 2 H, H2, H5), 4.27 (dd,  $J = 11.7$ , 4.9 Hz, 1 H, H1a), 3.82 (dd,  $J = 11.7$ , 7.1 Hz, 1 H, H1b), 2.10 (s, 6 H,  $2 \times \text{COCH}_3$ ), 2.07 (s, 6 H,  $2 \times \text{COCH}_3$ ), 2.03, 2.01 ( $2 \times$  s,  $2 \times$  3 H,  $2 \times \text{COCH}_3$ ) ppm.  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ , ref. to  $\text{CDCl}_3 = 77.16$ ):  $\delta = 170.6$ , 170.4, 170.1, 169.9, 169.60, 169.59 ( $6 \times \text{COCH}_3$ ), 131.4 (C7), 120.4 (C8), 72.5 (C6), 70.3 (C5), 68.0 (C3), 67.7 (C2), 67.3 (C4), 62.3 (C1), 21.0, 20.9, 20.9 ( $3 \times \text{COCH}_3$ ), 20.8 ( $3 \times \text{COCH}_3$ ) ppm. HRMS (+ESI-TOF): calcd. for  $\text{C}_{20}\text{H}_{28}\text{NaO}_{12}$  483.1478  $[\text{M} + \text{Na}]^+$ ; found 483.1477.

**L-glycero-D-gluc-oct-1-enitol (12):** Enitol **9b** (3.91 g, 18.8 mmol, 1.0 equiv.) was dissolved in water/acetone (50/50 mL), giving a slightly turbid solution. A small amount of Sudan red (III) in acetone was added, staining the mixture pink, and the reaction mixture was cooled with an external ice/EtOH bath. Ozone was bubbled through the reaction mixture through a sintered gas inlet. As soon as analysis by TLC ( $\text{CHCl}_3$ /MeOH/ $\text{H}_2\text{O}$  14:6:1) confirmed complete conversion of starting material to the target compound (with the slightly more apolar shadow; compare **1**) the ozone generator was switched off and oxygen was passed through the reaction for 30 min, after which  $\text{PPh}_3$  (10.5 g, ca. 2 equiv.) and additional acet-



one (50 mL, solubilising PPh<sub>3</sub> and facilitating fast reduction) were added and the mixture was stirred at room temp. overnight (no peroxides were detectable with peroxide test strips after 3 h). The reaction mixture was concentrated (200 mbar) and the aqueous residue (insoluble white solid) was washed with CH<sub>2</sub>Cl<sub>2</sub> and EtOAc (clear solutions), once with Et<sub>2</sub>O and once with hexane. The aqueous layer was filtered through a piece of cotton and concentrated, and coevaporation from MeOH gave crude material, with the target compound as the only species ( $\alpha/\beta$  ca. 43:57) according to <sup>1</sup>H NMR. The material solidified in a gum-like state; trituration in EtOH/Et<sub>2</sub>O (ca. 1:1, 100 mL) delivered a white solid (2.17 g, 51.1%,  $\alpha/\beta$  22:78) and the filtrate as an off-white solid (1.77 g, 41.6%,  $\alpha/\beta$  63:37), adding up to a total yield of 3.94 g (quant.) of pure **12**. Trituration of the combined solids from EtOH (40 mL + 2 drops of AcOH) over the weekend gave a white solid (3.11 g, 78%,  $\alpha/\beta$  1:20). Physical properties: m.p. >180 °C with decomp. (EtOH/H<sub>2</sub>O).  $[\alpha]_D^{28} = +51$  ( $c = 0.8$ , H<sub>2</sub>O, 48 h) [ref.<sup>[7a]</sup> m.p. 193–194 °C (aqueous ethanol).  $[\alpha]_D = +52$  ( $c = 1.9$ , H<sub>2</sub>O, final)}.  **$\beta$ -Anomer:** <sup>1</sup>H NMR (600 MHz, D<sub>2</sub>O, ref. to MeOH = 3.34):  $\delta = 4.59$  (d,  $J = 7.9$  Hz, 1 H, H1), 3.96 (td,  $J = 6.6$ , 1.4 Hz, 1 H, H6), 3.75–3.63 (m, 2 H, H7a/7b), 3.58 (app. t,  $J = 9.4$  Hz, 1 H, H4), 3.47 (app. t,  $J = 9.2$  Hz, 1 H, H3), 3.41 (dd,  $J = 9.8$ , 1.5 Hz, 1 H, H5), 3.22 (dd,  $J = 9.3$ , 8.0 Hz, 1 H, H2) ppm. <sup>13</sup>C NMR (151 MHz, D<sub>2</sub>O, ref. to MeOH = 49.5):  $\delta = 96.77$  (C1), 76.60 (C3), 75.04 (C5), 74.75 (C2), 69.64 (C4), 69.08 (C6), 63.20 (C7) ppm.  **$\alpha$ -Anomer:** <sup>1</sup>H NMR (600 MHz, D<sub>2</sub>O, ref. to MeOH = 3.34, out of mixture with  $\beta$ -isomer):  $\delta = 5.19$  (d,  $J = 3.77$  Hz, 1 H, H1), 4.00 (app. t,  $J = 6.6$  Hz, 1 H, H6), 3.80–3.74 (m, 1 H, H5), 3.73–3.63 [m, 2 H, H3, H7a, overlapping with H7a/7b( $\beta$ )], 3.62 (dd,  $J = 11.5$ , 5.5 Hz, 1 H, H7b), 3.55 (app. t,  $J = 9.6$  Hz, 1 H, H4), 3.51 (dd,  $J = 9.8$ , 3.8 Hz, 1 H, H2) ppm. <sup>13</sup>C NMR (151 MHz, D<sub>2</sub>O, ref. to MeOH = 49.5):  $\delta = 92.76$  (C1), 73.63 (C3), 72.07 (C2), 70.73 (C5), 69.90 (C4), 69.17 (C6), 63.56 (C7) ppm. HRMS (\*ESI-TOF): calcd. for C<sub>7</sub>H<sub>14</sub>NaO<sub>7</sub> 233.0637 [M + Na]<sup>+</sup>; found 233.0639. Calcd. C 40.00, H 6.71; found C 39.68, H 6.72.

**Preparation of Methyl Heptosides **14**:**<sup>[23a]</sup> The crude heptose **1** (<121.5 mmol) was taken up in MeOH (500 mL); a small amount of a white fine precipitate was filtered off (filter paper). A 5 mL aliquot was pumped through the reactor (QP-SA, 15 g) at 90 °C with 1 mL min<sup>−1</sup> flow rate and the product stream was analysed by TLC, showing a peak of material at 25–30 min and no material eluting before 20 min. A sample of the material was concentrated and analysed by <sup>1</sup>H NMR to show the expected ratio between targeted pyranoses and residual furanoses (ca. 93:7). The main amount (ca. 500 mL) was pumped through the reactor with a flow rate of 1 mL min<sup>−1</sup> at 90 °C and was collected in two pools; these were shown to be identical, confirming the stability of the reactor over the course of the reaction. The reaction mixture was concentrated, giving a white solid foam (1 mbar) that was dried in vacuo (27.7 g, quant. over two steps) and pulverized. The spectroscopic data (<sup>1</sup>H NMR) were consistent with the literature.<sup>[23a]</sup> A small sample (0.98 g) was stored; the rest was subjected to the acetylation/acetolysis step to afford **16a**.

**L-glycero- $\alpha$ -D-manno-Heptose Hexaacetate (**16a**):** Ac<sub>2</sub>O (130 mL, 1.4 mol, 12.0 equiv.) was added to crude methyl heptosides **14** (26.3 g, 117.2 mmol, 1.0 equiv.) and the heterogeneous mixture was stirred for several minutes, after which H<sub>2</sub>SO<sub>4</sub>/SiO<sub>2</sub> (1.6 mmol g<sup>−1</sup>, 500 mg, <0.01 equiv.) was added with external ice bath cooling. The temperature rose quickly to 75 °C, after which it started to cool down again. The violet solution was stirred for ca. 30 min, after which a small sample was concentrated and analysed by <sup>1</sup>H NMR to confirm complete acetylation and no acetolysis. Concentrated H<sub>2</sub>SO<sub>4</sub> (4 mL, 76.2 mmol, 0.65 equiv.) was added dropwise

at room temp. and the reaction mixture was stirred at room temp. overnight. Analysis of a small sample after 2 h indicated 60% conversion; the next morning full conversion was observed. The reaction mixture was cooled with an ice bath and neutralised by addition of DIPEA (32 mL, 2 equiv. relative to H<sub>2</sub>SO<sub>4</sub>) over a few minutes, with the colour changing from violet to orange (pH ca. 5–7). Stirring was continued for 10 min, after which the reaction mixture was diluted with EtOAc (450 mL), filtered (removing silica) and washed with water (2 × 200 mL), HCl (1 M, 100 mL, pH acidic) and water. The combined aqueous layers were back-extracted with fresh EtOAc (2 × 100 mL), the organic layers were washed with water, NaHCO<sub>3</sub> and brine and dried with Na<sub>2</sub>SO<sub>4</sub>, and the solvents were evaporated. The residue (ca. 80 g) was coevaporated from toluene and EtOH to give a very hard, solid crude material (60 g, was ground before drying). Recrystallisation from boiling EtOH (55 mL) gave white needle-shaped crystals within 1 h. The flask was stored overnight at room temp. and in the fridge for a day. The crystals were collected by filtration, washed with cold EtOH (2 × 25 mL) and dried to give pure  $\alpha$ -anomer (41.0 g, 75.5%, three steps from **9a**) as white crystals. The filtrate was concentrated and passed over a short plug of SiO<sub>2</sub> to give a syrup (9.9 g, 18%) with peracetates (pyranoses  $\alpha/\beta$  49:32 + 18%  $\alpha$ -furanoside) as the main components. Anomerisation in Ac<sub>2</sub>O/AcOH with H<sub>2</sub>SO<sub>4</sub>, workup as above and recrystallisation gave a second crop of pure **16a** (3.9, 7.2%) as a white solid. Physical properties: m.p. 131.0–132.0 °C (EtOH) [lit: 127–129 °C (Et<sub>2</sub>O/hexane)].<sup>[29]</sup>  $[\alpha]_D^{28} = +26$  ( $c = 1$ , CHCl<sub>3</sub>) {ref.<sup>[25]</sup>  $[\alpha]_D^{24} = +27$  ( $c = 1$ , CHCl<sub>3</sub>)}. <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>, ref. to CDCl<sub>3</sub> = 7.26):  $\delta = 6.08$  (d,  $J = 1.5$  Hz, 1 H, H1), 5.36–5.28 (m, 2 H, H4, H3), 5.28 (dd,  $J = 3.1$ , 1.8 Hz, 1 H, H2), 5.23 (ddd,  $J = 7.2$ , 5.1, 2.1 Hz, 1 H, H6), 4.25 (dd,  $J = 11.7$ , 5.1 Hz, 1 H, H7a), 4.16 (dd,  $J = 11.7$ , 7.3 Hz, 1 H, H7b), 4.12–4.08 (m, 1 H, H5), 2.18, 2.16, 2.13, 2.02, 2.01, 1.98 (6 × s, 6 × 3 H, 6 × COCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>, ref. to CDCl<sub>3</sub> = 77.16):  $\delta = 170.6$ , 170.4, 170.1, 169.9, 169.6, 167.9 (6 × COCH<sub>3</sub>), 90.8 (C1), 71.0 (C5), 69.1 (C3), 68.5 (C2), 66.9 (C6), 64.5 (C4), 62.3 (C7), 20.93, 20.90, 20.83, 20.78, 20.73, 20.70 (6 × COCH<sub>3</sub>) ppm. HRMS (\*ESI-TOF): calcd. for C<sub>19</sub>H<sub>26</sub>NaO<sub>13</sub> 485.1271 [M + Na]<sup>+</sup>; found 485.1270. Calcd. C 49.35, H 5.67; found C 49.49, H 5.68.

**Supporting Information** (see footnote on the first page of this article): Analysis of the compositions of crude compounds **5** and **9a–c** by <sup>1</sup>H NMR spectroscopy, the optimisation of the flow conditions for the preparation of **14** and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of all purified compounds.

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